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215. A nucleic acid encoding the antibody or functional fragment of any of claims 1-3, 4, 5, 6, 7 or 129-214.

REMARKS

Claims 56-128 are pending. Claims 56-73, 77-104 and 107-109 are canceled herein without prejudice to Applicant pursuing the subject matter of these claims in a related application. Claims 111-128 have been canceled and rewritten as new claims 129-210. Claims 105 and 106 have been amended. New claims 129-215 have been added. Upon entry of the amendment, claims 56-59, 66-68, 70-72, 74-76, 78, 79, 105, 106, 110 and 129-215 will be pending. Support for the amendments and new claims can be found throughout the specification and the claims as filed. Claims 105 and 106 have been amended to correct antecedent basis. Support for new claims 129-210 can be found, for example, in the claims as filed and on page 39, line 17, to page 45, line 24. Support for new claims 211-214 can be found, for example, in original claim 56 and on page 6, lines 1-10, Figure 2, page 16, lines 10-17, and page 16, line 30, to page 17, line 14. Support for new claim 215 can be found, for example, in original claims 78 and 79 and on page 45, line 25, to page 46, line 12. Accordingly, these amendments and new claims do not raise an issue of new matter and entry thereof is respectfully requested.

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Applicant has set forth the amendment to the claims in clean form above and in Appendix A, with marked up amendments indicated with brackets and underlining.

New claims 129-210 merely separately claim members of the Markush groups of claims 110 and 127, which had no prior art or § 112 issues indicated in the Office Action. For the convenience of the Examiner, attached as Appendix B is a table of correspondence between previously pending claims 111-128 and new claims 129-210.

Objection to the Abstract

In the Office Action, the Abstract has been objected to because it exceeds 150 words. Applicant has amended the Abstract to less than 150 words. Therefore, Applicant respectfully requests that this objection be withdrawn.

Applicant acknowledges that the enablement rejection regarding deposit of biological materials has been removed. However, Applicant respectfully maintains the position of record set forth in the response mailed on October 10, 2001.

Rejection Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 80-96 and 109 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed. Claims 80-96 and 109 have been canceled without prejudice to pursuing the claims in a continuation

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application. Therefore, this rejection has been rendered moot, and Applicant respectfully requests that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 56-85 and 105-107 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed. Applicant points out that this rejection has been rendered moot with respect to claims 56-73, 77-85 and 107 since these claims have been canceled.

With respect to claims 74-76 and amended claims 105 and 106, Applicant points out that the term "enhanced" is not recited in these claims. These claims specifically recite that the claimed antibodies have higher affinity relative to parental LM609 grafted antibody. Therefore, Applicant respectfully requests that this rejection be withdrawn.

With regard to the claims reciting the term "enhanced," Applicant maintains, for the reasons of record set forth in the responses mailed January 18, 2001, and October 10, 2001, that the claims reciting this term are clear and definite. Nevertheless, to further prosecution, claims reciting the term "enhanced" have been canceled. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

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Rejection Under 35 U.S.C. § 102

The rejection of claims 56-59, 62, 65-68, 70-75 and 77 under 35 U.S.C. § 102(e) as allegedly anticipated by Brooks et al., U.S. Patent No. 5,753,230, is respectfully traversed. Applicant points out that this rejection has been rendered moot with respect to claims 56-59, 62, 65-68, 70-73 and 77 in view of the cancellation of these claims.

Applicant maintains that the claimed grafted antibodies are novel over Brooks et al. Applicant points out that claims 74 and 75 do not recite the phrase "enhanced LM609 antibody." Claims 74 and 75 are directed to high affinity LM609 grafted antibodies having higher affinity relative to parental LM609 antibody. In contrast, Brooks does not teach the claimed high affinity LM609 grafted antibodies having at least one amino acid substitution in one or more CDRs of heavy or light chain variable regions referenced as SEQ ID NOS:6 and 8, respectively. Brooks et al. provides no teaching of the structural characteristics of the sequences specifically recited in the claims. Furthermore, Brooks et al. provides no teaching on antibodies having higher affinity than parental LM609 antibody. Absent such teachings, Brooks et al. does not teach every element of Applicant's claimed invention and therefore cannot anticipate these claims. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Regarding the claims reciting the phrase "enhanced LM609 antibody," Applicant maintains, for the reasons of record

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set forth in the responses mailed on January 18, 2001, and October 10, 2001, that Brooks et al. does not teach the claimed grafted antibodies. Nevertheless, to further prosecution, claims reciting the phrase "enhanced LM609 antibody" have been canceled. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

With regard to new claim 211 and dependent claims 212-214, claim 211 is directed to a grafted antibody exhibiting selective binding affinity to $\alpha_v\beta_3$, or a functional fragment thereof, comprising one or more CDRs having at least one amino acid substitution in one or more CDRs of the heavy chain variable region polypeptide referenced as SEQ ID NO:6 or the light chain variable region polypeptide referenced as SEQ ID NO:8, the antibody or functional fragment thereof having increased integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity relative to parental antibody comprising a heavy chain variable regaion polypeptide referenced as SEQ ID NO:6 and a light chain variable region amino acid sequence referenced as SEQ ID NO:8.

In contrast to new claims 211-214, Brooks et al. does not teach the claimed grafted antibodies having one or more CDRs having at least one amino acid substitution in one or more CDRs of SEQ ID NOS:6 and 8 and having <u>increased</u> integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity relative to parental antibody comprising a heavy chain variable region polypeptide referenced as SEQ ID NO:6 and a light chain variable region amino acid sequence

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referenced as SEQ ID NO:8. Furthermore, Brooks et al. does not teach any of the structural features of LM609, let alone the sequences recited in the claims as specific SEQ ID NOS. Thus, Brooks et al. does not teach every element of the claimed invention. Accordingly, absent a teaching of every element of the claimed invention, Applicant respectfully submits that Brooks et al. cannot anticipate new claims 211-214.

Rejection Under 35 U.S.C. § 103

The rejection of claims 56-59, 62, 66-68, 70, 71 and 74-76 under 35 U.S.C. § 103 as allegedly obvious over Brooks et al., U.S. Patent No. 5,753,230, in view of known gene cloning and expression strategies is respectfully traversed. Applicant points out that this rejection has been rendered moot with respect to claims 56-59, 62, 66-68, 70 and 71 in view of the cancellation of these claims.

Applicant maintains that the claimed grafted antibodies are unobvious over Brooks et al., alone or in combination with known gene cloning and expression strategies. Applicant points out that claims 74-76 do not recite the phrase "enhanced LM609 antibody." Claims 74-76 are directed to high affinity LM609 grafted antibodies having higher affinity relative to parental LM609 antibody. In contrast, Brooks does not teach or suggest the claimed high affinity LM609 grafted antibodies having at least one amino acid substitution in one or more CDRs of heavy and light chain variable regions referenced as SEQ ID NOS:6

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and 8. Brooks et al. provides no teaching or suggestion of the structural characteristics of the sequences specifically recited in the claims. Furthermore, Brooks et al. provides no teaching or suggestion of antibodies having higher affinity than parental LM609 antibody. Absent such teachings or suggestions, the claimed antibodies are unobvious over Brooks et al.

With regard to new claims 211-214, Applicant respectfully submits that Brooks et al., alone or in combination with known methods of gene cloning or any of the references Queen et al. (U.S. Patent No. 5,585,089), Rosok et al. (J. Biol. Chem. 271:22611-22618 (12996)), or Glaser et al. (J. Immunol. 149:3903-3913 (1992)), does not teach or suggest all the elements of the claimed grafted antibodies. Brooks et al., alone or in combination with known methods of gene cloning, does not teach or suggest the structural characteristics specifically recited in the claims and therefore does not teach or suggest every element of the claimed invention. Furthermore, Brooks et al., alone or in combination with known methods of gene cloning, does not teach or suggest the claimed grafted antibodies having one or more CDRs having at least one amino acid substitution in one or more CDRs of SEQ ID NOS:6 and 8 and having increased integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity relative to parental antibody comprising a heavy chain variable region polypeptide referenced as SEQ ID NO:6 and a light chain variable region amino acid sequence referenced as SEQ ID NO:8. Absent such a teaching or suggestion, Applicant maintains that the claimed grafted antibodies are unobvious over Brooks et al., alone or in combination with known

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methods of gene cloning. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Double Patenting Rejection

The provisional rejection of claims 56-59, 62, 65-68 and 70-77 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-18 and 26-31 of co-pending application serial No. 08/790,540 and claims 1-8, 15-26 and 33-42 of co-pending application serial No. 08/791,391 is respectfully traversed. Applicant points out that this provisional rejection has been rendered moot with respect to claims 56-59, 62, 65-68, 70-73 and 77 in view of the cancellation of these claims.

With regard to claims 74-76, Applicant respectfully submits that the claimed high affinity LM609 grafted antibodies are patentably distinct from the claims in either of copending application serial Nos. 08/790,540 or 08/791,391. The claims in either of application serial Nos. 08/790,540 or 08/791,391 are not directed to a high affinity LM609 grafted antibody comprising one or more CDRs having at least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide referenced as SEQ ID NO:6 or a LM609 grafted light chain variable region polypeptide referenced as SEQ ID NO:8, as claimed in the subject application. Furthermore, the claims of application serial Nos. 08/790,540 or 08/791,391 are not directed to claims reciting SEQ ID NOS of CDRs having at least one amino acid substitution and higher affinity relative to parental LM609

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grafted antibody. Therefore, Applicant maintains that claims 74-76 of the present application are unobvious over the claims of application serial Nos. 08/790,540 or 08/791,391. Accordingly, Applicant respectfully requests that the provisional double patenting rejection be withdrawn.

The provisional rejection of claims 56-128 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-18 and 26-31 of co-pending application serial No. 09/339,922 is respectfully traversed. Applicant points out that claims 1-18 and 26-31 of application serial No. 09/339,922 were canceled in the response filed on August 2, 2002. In light of the cancellation of these claims, Applicant respectfully submits that this provisional rejection has been rendered moot and requests that this provisional rejection be removed.

Applicant respectfully points out that the provisional obviousness-type double patenting rejection of claims 110-128 over claims 1-18 and 26-31 of U.S. serial No. 09/339,922 was the only rejection of these claims. In light of the cancellation of claims 1-18 and 26-31 in U.S. serial No. 09/339,922 and obviation of this provisional double patenting rejection, claim 110 and new claims 129-210, which correspond to previous claims 112-128, should be allowable.

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CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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Date

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